FOETAL PHARMACOLOGY

Drugs and the Unborn Child

by our Special Correspondent

SOME pregnant women are probably consuming drugs unnecessarily, to the detriment of their future offspring. This warning from several speakers at a symposium in New York on March 15 and 16 was underlined by the revelation of general ignorance of many of the effects of drugs on the human foetus. The occasion was a gathering of representatives of all disciplines associated with human development, brought together by the March of Dimes to discuss recent advances and unsolved problems concerning drugs and the unborn child. As the meeting progressed, however, unsolved problems predominated the proceedings, and it became clear that it is by no means simple to identify a particular drug as a potential hazard to the foetus.

The voracity of pregnant women for drugs is well illustrated by a retrospective study of 911 women in Edinburgh, reported by Dr J. O. Forfar (University of Edinburgh). His team found that, excluding iron, drugs were prescribed for 82 per cent of the women during pregnancy, with an average of four drugs each. Sixty-five per cent of the women took non-prescription drugs, mostly aspirin and antacids. The survey revealed a tendency to administer certain drugs—antibiotics, cough medicine, iron and tranquillizers—throughout pregnancy; others—antiemetics, antihistamines, appetite suppressants, bronchodilators and hormones—early in pregnancy; and others—for example, antacids, analgesics, barbiturates, diuretics and hypnotics—late in pregnancy. Dr Forfar's conclusion that the basis on which many of these drugs were used could be questioned, was echoed by Dr L. Stern (McGill University). He wondered whether, for example, all the pregnant women who took thalidomide, and later gave birth to severely malformed babies, had really needed the drug as treatment for insomnia.

Other speakers urged great care in the prescribing of drugs during pregnancy. But the situation for the physician is often not clear cut, as was explained by Dr L. M. Hellman (US Department of Health, Education and Welfare). The value of a drug must be measured according to the ratio of benefit to safety, which makes it very difficult for anybody to rule that a particular drug should never be given to pregnant women. For example, some attention at the symposium focused on diphenylhydantoin ('Dilantin'), which is suspected sometimes to cause birth defects such as cleft palate. But 'Dilantin' is an important anti-convulsant drug, which is given to pregnant women as a treatment for epilepsy. As epileptic seizures must obviously be avoided during pregnancy it would be rash immediately to ban or restrict the use of this drug.

Faced with such problems, the physicians turn for information to the experimentalists, who are beset with problems of their own. The effects of drugs on the foetus can only be assessed in comparison with the normal sequence of changes involved in biochemical development. At present little is known about the situation in the human foetus, and so it was not surprising that contributors to the biochemical sessions of the meeting concentrated on reviewing data obtained with rodents and other animals. Dr O. Greengard (Harvard University), for example, reported progress with the rat, revealing that four different groups of enzymes, induced by various hormones, appear at four different stages of foetal development. Unfortunately, as data slowly amass, it becomes increasingly clear that the human foetus, far from resembling the rat, is biochemically unique in its development. Dr D. B. Villee (Harvard University) reported that the biosynthetic pathway of the steroid hormones in the human develops quite differently from that in other species. This underlines one of the greatest problems of students of drug metabolism—the paucity of suitable animal models that can be trusted to parallel the situation in the human foetus. The baboon, however, offers some hope as a model for the study of foetal steroid metabolism, according to Dr S. Solomon (McGill University).

Summarizing the many goals of developmental pharmacologists, Dr B. L. Mirkin (University of Minnesota) gave highest priority to the study of the passage of drugs into the foetal environment throughout gestation; the effects of drugs on normal development; the influence of postnatal maturation on drug disposition; and inherited and acquired factors influencing the action of drugs. Increased

A Common Receptor for Hallucinogens?

IT is always the hope that elucidating the mechanisms of hallucinogenic drugs will give clues as to the nature of mental disorders and ways of developing treatment. Psychopharmacologists would no doubt be delighted to find that hallucinogens operate by way of a common effect.

Szent-György's group have studied several psychoactive compounds and suggested that their action might result from their powerful ability to donate electrons (*Science*, **130**, 1191; 1960). Snyder and his co-workers have found a high correlation between the potency of hallucinogens and their willingness to give up electrons (*Proc. US Nat. Acad. Sci.*, **54**, 258; 1965). Three dissimilar classes of drugs have been found to produce psychedelic effects—lysergic acid diethylamide (LSD), derivatives of tryptamine, and compounds related to phenylethylamine. Theoretical calculations showed that within each class, the agents which can best donate electrons are those with the greatest hallucinogenic effect in man. A later study showed that the psychoactive drugs in each group are capable of assuming conformations analogous to some part of the ring structures of LSD (*Proc. US Nat. Acad. Sci.*, **60**, 206; 1968).

Some experimental support for these theoretical studies has been provided by Smythies *et al.* (*Nature*, **226**, 644; 1970), who found that THPC (which represents the D ring of LSD) will antagonize the behavioural effects of LSD, but greatly potentiates the effect of mescaline, which is a phenylethylamine resembling the A and B ring portion of LSD. This suggests that mescaline occupies part of the site acted on by LSD, but that the complete structure is necessary for the full effect.

In the forthcoming issue of *Nature New Biology* (April 11), Smythies's team now report that behavioural effects of two amphetamine derivatives support the notion of a common site of action. Using an animal behaviour task (Sidman avoidance), they compared the psychomimetic activity of stereoisomers of 2,5 dimethoxy-4-bromoamphetamine (DOB) and 2,5 dimethoxy-4-methylamphetamine (DOM). Their reasoning was that if these two amphetamine derivatives, which show profound psychoactivity in man, act by way of a LSD-type receptor, then their R(−) isomers should have the greater effect because the R(−) conformation corresponds to that of LSD. The stereospecific approach is powerful because it controls for variations in the transport and metabolism of drugs. Presumably, only specific receptor sites would differ in their response to the subtle steric differences between the two isomers. In these experiments, the R(−) isomers of both DOM and DOB were considerably more active than the alternate S(+) configuration.

If subsequent investigations continue to support the notion of a common receptor for hallucinogenic drugs, then the central question will be: what is the endogenous neurochemical which is the true substrate for the "hallucinogenic receptor"?